REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 1, 11 and 25 have been amended. Claims 1-46 are in the case and are before the Examiner.

A. The Amendments

Claims 1, 11 and 25 have been amended to recite a preferred percentage of conservative substitution of residues in an HBc sequence. Specific support for those amendments can be found in the specification at pages 73-75. Claims 1, 11 and 25 have also been amended to positively recite the presence of a cysteine residue at HBc position 61 as is recited near the bottom of page 19 of the specification.

Claim 25 has been amended to clarify that the added sequence of Domain II sub-paragraph (a)(i) and (b)(i) are a heterologous sequence. Specific support for this amendment can be found at least at pages 15-17, 30-33, 37-43, and 51-52. Claim 25 has been amended to conform the language reciting the "linker-containing sequence" to that of claims 1 and 11. Additional support can also be found at least at pages 14, 15, 18 and 31 of the specification. Claim 25 has also been amended to clarify that the enhanced stability is measured by size exclusion chromatography. This amendment is supported at least by the description of Fig. 4, the specification at pages 147-149 and 180-196.

It is thus seen that no new matter has been added.

B. Rejection Under 35 USC §112, Second Paragraph

The Action noted that the rejections under 35 USC §112, Second Paragraph were withdrawn in part and maintained in part. Unfortunately, whereas the previous Action used numbered paragraphs to specify its rejections, the present Action has not done so making it difficult to be certain that remaining specific bases for have been dealt with. In addition, the Action appears to be of the view that the claims had to be amended to be properly responsive, and that cannot be agreed with. Nonetheless, the withdrawal of the rejections related to "optionally", "conservatively substituted", "substantially", "of at least about' and "up to about" arte noted with appreciation. It is believed that the remaining identifiable bases for rejection have also been overcome as is discussed below.

Former Paragraph 1

The prior Action rejected claims 1, 11 and 25 because of their use of the word "or" was said to render them subject to numerous possibilities. It is submitted that current US practice permits the use of "or" in claims, and that the present use does not render the claims indefinite. Should this basis for rejection be maintained, it is requested that specificity as to the alleged indefiniteness be stated.

Former Paragraph 2

In regard to claim 1 part (b)(i), discussed in former Paragraph 2, the action asserts that it makes no sense to say zero residues are present and asks if none are present, what is peptide-bonded to the one of about 245 amino acids? Zero residues present is simply one extreme and if no residues of that region are present, one need only to note that residue 75

is present at the C-terminus of the sequence so that is the residue to which an insert would be bonded. The Examiner's attention on this point is directed to the full paragraph on page 63.

Former Paragraph 5

The prior Action asserted a lack of clarity as to which sequence one uses to determine a conservative substitution. While not agreeing to the presence of any lack of clarity, the prior Reply amended the claims to recite a comparison to the sequence of SEQ ID NO:1. It is therefore not understood why this basis for rejection is still present and it is requested that the Examiner provide further clarification of this rejection if it is maintained.

Former Paragraph 6

An ambiguity was asserted to be present in claim 25, in the subsection dealing with Domain IV and the number of arginines and lysines that could be present. That sub-paragraph was amended to provide added clarity and explained to mean exactly what it said. It appears, however, that the basis for rejection has been maintained. It is again requested that an explanation be provided as to the basis for maintaining the rejection should it be repeated.

Former Paragraph 8

The Action maintained the rejection relating to use of the phrase "more stable" in view of the explanation provided in the specification. The present amendments recite that "more stable" is determined using "size exclusion chromatography". It is thus believed that the rejection is moot.

Prior Paragraph 10

A potential ambiguity in claim 25 was noted and the prior Reply amended the claim to avoid that possibility. If this rejection is maintained, it is requested that a further explanation be provided as to the basis for maintaining the rejection.

New Rejection

The present Action has asserted that claim 25 was indefinite because of its recitation of "an immunogen-containing sequence". The Action noted that that recitation could mean a native or a heterologous sequence. It is believed that this rejection is moot in view of the present amendments.

C. Rejection Under 35 USC §112, First Paragraph

All of the claims were again rejected under the first paragraph of Section 112 as allegedly failing the description requirement and the enablement requirement. These bases for rejection cannot be agreed with and are respectfully traversed to the extent that they are asserted in view of the present amendments.

Turning first to the description requirement, although it cannot be agreed that the claims were not within the written description, the claims have been amended to further limit the percentage of possible substitutions and to recite their locations. It is thus submitted that the rejection is moot.

The Examiner's attention is also invited to the disclosures of US Patent No. 6,964,769 to Sebbel et al., that just came to counsel's attention as discussed hereinafter. Claim 1 and all of the dependent claims of that presumptively

valid patent recite a named polypeptide sequence "or a sequence having at least 90% sequence identity to said polypeptide sequence . . ." Counsel was unable to find any disclosure as to the identity of the up to 10% substituting residues, as compared to the lower percentage of substitutions in the amended claims herein. It is thus submitted that the present claims define a more limited number of chimers than those of the presumptively valid issued patent that claims similar, but different chimers. It is submitted that the applicants were in possession of a very large number of the desired chimer molecules as of the filing date, and that this portion of the rejection should be withdrawn.

The Action's conclusions regarding the alleged lack of enablement also cannot be agreed with on several grounds. First, the Action relies on two cases as foundations for its conclusion, and both may now be decided differently based on the same facts.

The first relied-on case was *In re Fisher* 166 USPQ 18, 24 (CCPA 1970), in which the Court held that a claim to a synthetic ACTH peptide having at least 24 amino acid residues and reciting that residues 25-39 were unnecessary was not enabled because no one knew how to make or obtain the full length peptide with 39 residues. The application in *Fisher* was filed in November of 1960, several years prior to the publication of the seminal paper by Nobel Laureate R.B. Merrifield in 1963 that first disclosed solid phase peptide synthesis. [Merrifield, *J. Am. Chem. Soc.*, **85**:2149-2154 (1963), copy enclosed.] Today, or in 2003 when the present application was filed, the result would likely be different as workers of ordinary skill routinely prepare 40-mer peptides. Similarly, a skilled worker in 2003 could prepare substantially any desired

protein, particularly those disclosed and claimed here. Thus, although the law recited in *Fisher* is still good, it should not be applied here because the underlying facts are different, and this basis for rejection should be withdrawn.

Similarly, the second relied-on case, *Colbert v. Lofdahl*, 21 USPQ2d, 10658, 1071 (BPAI 1992) has been eclipsed by the change in the law regarding acts abroad being used to support conception and reduction to practice in an interference. The holding of that case has also been undercut by the holding in *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 323 F3d. 956 (Fed. Circ. 2002) that permitted a recitation of Budapest Treaty deposit information for a non-sequenced nucleic acid to be in compliance with the description requirement. Thus, had Lofdahl made such a deposit, his application could have been in compliance with both the description requirement and enablement requirements of Section 112. This basis for rejection should again also be withdrawn.

The Action also discounts the knowledge imparted by the cited prior art regarding use of the several subtypes of HBV by asserting that the art has used a "specific and well known strain of HBV, . . .". However, The Pumpens 1995 paper teaches at page 69 "HBc proteins belonging to HBV genomes with different HBsAg subtypes, such as *adw*, *ayw*, *adyw* and *adr*, have been used as carriers. [internal citations omitted]"

The Court in *Capon v Eshhar*, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005) noted that

> [p]recedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science and technology, the

> predictability of the aspect at issue and other considerations appropriate to the subject matter. [Citation omitted.]
> - - - - - - - - - -
> It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect insufficiently demonstrated to characterize a generic invention. [Citing *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976).]

The *Angstadt* case dealt with a catalyst complex molecule that contained a transition metal cation from one of several Groups of the Periodic Table, an undisclosed "inorganic anion" for the metal cation, and a hexaalkylphosphoramide whose six alkyl groups contained one to thirty carbon atoms in each alkyl group. The metal salt (cation plus anion) was said to be present at 1-4 moles per molecule and the hexaalkylphosphoramide was present at 1-8 moles per molecule complex.

Footnote 2 of *Angstadt* noted that the Solicitor asserted that the claim read on thousands of compounds including "any one of at least 50 metal cations combined with any inorganic anion". Actually, "thousands" was a gross underestimate.

For example, there are eight $C_1$-$C_4$ alkyl groups; i.e., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and iso-butyl. So, for the hexaalkylphosphoramidates where the alkyl groups are $C_1$-$C_4$, there are $8^6$ or 262,144 different phosphoramidates, omitting possible chiral isomers. Multiplication by the number of cations, anions and ratios (1-4:1 salt and 1-8:1 hexaalkylphosphoramide per molecule) skyrockets the number of compounds just for that relatively small number of alkyl groups.

According to Noller, Chemistry of Organic Compounds, W.B. Saunders Company, Philadelphia, 1951, page 35, (copy enclosed and noted on Form PTO SB/08A) there are over 4 billion $C_{30}$ alkanes alone. Presuming the number of $C_{30}$ alkyl groups is about the same as the number of alkanes, which is a gross undervaluing as there are 15 straight chain $C_{30}$ alkyls alone, the *Angstadt* formula actually therefore encompassed an astronomical number of separate compounds once all of the anion, cation, alkyl group and ratio permutations encompassed by the claims are taken into account. For example, there would be about $(4 \times 10^9)^6$ or $(4096 \times 10^{54})$ different $C_{30}$ hexaalkylphosphoramides alone. That number of compounds exceeds any arbitrarily large number that one could pick from the physical world such as the number of atoms in the earth if it were all iron [(mass = about $6 \times 10^{27}$g/55.6g/mole) X $6.023 \times 10^{23}$ atoms/mole = about $6.5 \times 10^{49}$ atoms] or the more chemically familiar Avagadro's Number of $6.023 \times 10^{23}$ molecules per mole.

The *Angstadt* inventors disclosed just 40 examples, with one compound that did not work in their process. The Court there held that the inventors did not have to make and test every compound in their claims, nor did every compound have to work.

That Court went on to discuss the disclosure that there taught how to make and how to use a claimed catalyst. It continued that if a skilled worker wanted to make another catalyst than those specifically disclosed in the 40 examples that worker could simply follow the disclosure and make a desired catalyst compound. It further pointed out that the catalysis process was not complicated and needed no special conditions nor equipment. The *Angstadt* claims were found to be

enabled despite the amazingly large number of catalysts encompassed.

That Court went further in saying that some "experimentation" was permitted and held that the key phrase was "undue", not "experimentation". Practicing of that invention "would not 'require ingenuity beyond that to be expected of one of ordinary skill in the art' ... ", at 218 (citation omitted). The same should be the case here.

*Angstadt* dealt with synthetic organic chemistry. The present application deals with biochemistry relating to HBc chimers. As noted previously, from *Angstadt* and the art already of record, skilled workers knew how to make and use the constructs claimed here at the time the application was filed. It is submitted that given the several examples and citations in the specification the claimed invention was enabled and this basis for rejection should be withdrawn.

The Action asserted that if one were to use a computer program for guidance in determining which amino acids can be substituted, inserted or deleted without abolishing biological activity or particle formation, the instant invention should have been anticipated by the technology of a computer program such as LASERGEN. That assertion is believed to be incorrect for at least three reasons as applied here.

First, the claims have been amended to provide even more guidance to the skilled worker in determining which residues to alter.

Second, the hypothesis laid out of using a computer to anticipate the claimed subject matter has not in fact been done and is therefore moot, as well as being repudiated by the Court when it discussed the so-called Von Bremer Doctrine in *In re*

*Hoeksema*, 158 USPQ 596 (CCPA 1968). In discussing *Von Bremer*, the Court stated

> [t]o the extent that anyone may draw an inference from the Von Bremer case that the mere printed conception or the mere printed contemplation which constitutes the designation of a "compound" is sufficient to show that such a compound is old, regardless of whether the compound is involved in 35 USC §102 or 35 USC §103 rejection, we totally disagree. 158 USPQ at 600, quoting from *In re Brown*, 141 USPQ 245, at 247 (CCPA 1964).

It is again submitted that this basis for rejection should be withdrawn.

Paragraph 41 of the present Action also points out that

> [i]t is known in the art of protein chemistry that the modifications are generally chosen so as not to destroy the conformation of the protein, and in the case of particle-forming proteins the modifications are generally chosen so as not to destroy the particle-forming ability of the protein (citation omitted).

The Action thus contradicts itself in asserting that a skilled worker could not make and use the claimed invention to its claimed breadth and then later asserts that skilled workers know how to modify proteins so that they maintain conformation and ability to form particles. It is submitted that the views expressed I Paragraph 41 of the Action are correct.

The Action has continued to place great reliance upon the disclosures of a 30-year old peptide hormone paper by Rudinger, which was cited in the Action for the proposition that even one amino acid can make a major difference in the function

of a molecule. As was noted previously, being out of date and dealing with an entirely different type of subject matter, the Rudinger paper is inappropriate for this discussion and is non-analogous art. The Action also asserts that

> [t]here is no reference indicating that the current knowledge on how to develop virus-like particles (VPL) using HBc can be readily applied to any undefined sequences, such as sequences that are 80 or 90% identical to SEQ ID NO:1, and have reasonable expectation of success that such undefined sequences can form stable VPL.

It is respectively submitted that the before-discussed Pumpens 1995 paper and US Patent No. 6,964,769 that has just recently come to the attention of applicants and counsel are two such documents. In addition, the Court in *In re Marzocchi & Horton*, 169 USPQ 367, 369-370 (CCPA 1971) held that the

> "only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion [of efficacy]." [169 USPQ at 369; emphasis in the original.]
>
> The Court went on to hold:
>
> "it is incumbent upon the Patent Office, whenever a rejection on this basis [doubt as to enablement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate statement." (Emphasis in the original.)

The *Marzocchi* requirement of an explanation of "why" truth or accuracy of the disclosure is doubted has not been

complied with by placing reliance on the Rudinger disclosures that have no specificity toward HBc chimers as compared to the contrary teachings of the Pumpens paper or the assertions of Paragraph 41 of the Action, and the specification and its other citations. Still further, the Action has provided no basis for asserting that any of the other disclosed HBc proteins would respond differently from that used as illustrative. This rejection should therefore be withdrawn.

D. Rejections Under 35 USC §102(b)

Withdrawal of the rejection of claims 1 and 11 under 35 USC §102(b) over the disclosures of Zlotnick is noted with appreciation. The rejection of claim 25 over those teachings is maintained and is respectfully traversed.

The Action asserted that the native immunogenic sequence of HBc could be the immunogenic sequence recited to be present in Domain II (a)(i) and (b)(i). It is respectfully submitted that if that were the case, the claim would be indefinite under the Second Paragraph of Section 112 for double inclusion of a limitation. Rather, the recited immunogenic sequence was intended to be a heterologous sequence as was understood for the "optional immunogenic epitope sequence an [D]omain I . . ." The present amendments insert the word "heterologous" to clarify the issue.

It is also noted that Zlotnick discloses no sequence in which the Cys at position 61 is present whereas the Cys at one or both of positions 48 and 107 is absent absent. The present amendments have clarified this point for all of the claims.

It is therefore believed that this basis for rejection is moot and should be withdrawn.

E. Rejection Under 35 USC §102(a)

Claims 25, 27-28, 30, 32 and 43-46 were again rejected as allegedly anticipated by the teachings of the paper by Jegerlehner et al. (2002) (hereinafter Jegerlehner). It is continued to be thought that Jegerlehner does not disclose a chimer contemplated by the present or prior claims, so this rejection is respectfully traversed.

The Action asserts that the "claimed chimer in claim 25 does not require Cys at either N-terminus or C-terminus," and went on to characterize a claimed chimer and the materials taught by Jegerlehner. Unfortunately, the quoted language is believed to be incorrect, as was the characterization of the Jegerlehner construct.

Thus, the relied-on construct was said to contain

> zero to one cysteine in HBc domain I and IV, native Cys 107 is replaced, a Gly-Gly-Lys-Gly-Gly linker-containing sequence is replaced at positions 79-80 of domain II, and finally, HBc/M2 chimer have three cysteine residues in M2 sequence present in domain II (see 2.6, column 1, p.3106).

It is submitted, however, that a chimer of claim 25 must have at least one Cys either in Domain I or Domain IV as is recited in the phrase following the sub-paragraphs of Domain IV quoted below

> "(ii) having at least one cysteine residue present from the recited zero to three cysteine residues of Domains I and IV, and"

The Jegerlehner construct recited in the Action has three Cys residues on a hapten linked to the "Gly-Gly-Lys-Gly-Gly linker" in Domain II. That construct has no added cysteine residue at the N-terminus or C-terminus as is claimed. As such, this rejection should again be withdrawn.

F. Rejections Under 35 USC §103(a)

1. First Rejection

Claims 2, 4-6, 16-22, 30-39 and 43-46 continue to be rejected as allegedly obvious from the disclosures of Zlotnick (1997) above and Pumpens et al. (1995), hereinafter Pumpens. The present Action defends the prior Action and misconstrued the prior Reply. This rejection is respectfully traversed.

The prior Reply concentrated only on the use in the Action of data from Table 1 of Pumpens and made no comment about Table 3 other than to mention reliance upon it. The conclusion that "the stability behavior of truncated HBc molecules are so different from full length molecules that the latter are not predictive of the former" is maintained.

The prediction that the prior Action made was that combining the teachings of Pumpens and Zlotnick would be appropriate and would result in leading a skilled worker to the claimed invention. Rather, that combination is only made by a hindsight reconstruction of the present claims in a manner contrary to their intended meaning as illustrated in the present amendment regarding the Cys at position 61 and is self-contradictory.

Thus, as has been noted before, Zlotnick teaches constructs in which the cysteines at positions 48, 61, and 107 are all absent and replaced by alanines, with and without a Cys added at position 150. Those were the constructs named Cp*149

and Cp*150, respectively. Thus, even if one were to sum the teachings of Zlotnick with those of Pumpens, the resulting construct would have either all three Cys residues at positions 48, 61 and 107, or only have no Cys residues at those positions. Each such construct is different from that claimed. As such, this basis for rejection should be withdrawn as there is no teaching that leads to what is and was claimed.

Furthermore, the Pumpens teaching that asserts that foreign epitope insertions into the HBc sequence "exert a stabilizing effect on chimeric HBCΔ derivatives . . ." is antithetical to replacing the cysteines at each or both of positions 48 and 107, and adding a N-terminal or C-terminal Cys to a HBc chimer to gain increased stability. If insertions stabilize, why replace the internal Cys residues or add a terminal Cys?

On the other hand, Zlotnick says nothing about the effect of insertions on stability. As has been shown in the present application and in the applications of Dr. Birkett of record herein, those insertions destabilize the chimer particles and an added terminal Cys is needed for better stability. None of those earlier applications of Dr. Birkett teach or suggest gaining stability be replacement of internal Cys residues.

The present Action went to great lengths to explain away the prior Action's mis-use of the word "linker" from the reference to Pumpens at page 69, column 1, last paragraph, for a disclosure of "a heterologous linker residue for a conjugated epitope present in the HBC (sic) immunodominant loop." It is respectfully submitted that the immunological marker sequence is <u>not</u> a "linker" as that word is used in the phrase of claims 1 and 11 and now 25 ("sequence containing a chemically-reactive linker residue for a conjugated hapten").

The present Action notes that Pumpens asserts that particles formed from C-terminal truncated HBc proteins are less stable that are the particles made from non-truncated proteins. Pumpens cited three papers for that proposition after making the statement, and applicants agree with that proposition as it forms one basis for their invention. The prior Reply disagreed with reliance on the remainder of the Pumpens page 67 disclosure in which unpublished work by Borisova was relied on for the statement "foreign insertions are not only possible but also exert a stabilizing effect on chimeric HBcΔ derivatives especially in the case of internal insertions [Borisova unpubl.]"

It is submitted that citations normally follow the statement for which they are giving credit. As such, the three citations go with the lack of stability particles made from C-terminal truncated proteins, and the Borisova citation goes with the enhanced stability for sequences with internal insertions.

The present Action has thus not cured the deficiencies of the prior Action in its characterization nor has it shown how a worker of ordinary skill looking forward at the time of filing here would have known what to keep and what to throw out of the Pumpens and Zlotnick disclosures to come up with the present invention. It is submitted that just as Section 112, First Paragraph, requires that the applicant must mark a trail through the woods by supplying blaze marks on trees [*In re Ruschig*, 154 USPQ 118, 122 (CCPA 1967)], an assertion of obviousness must also contain blaze marks for the skilled worker to find his/her way through the forest to the tree of the claims. It is respectfully submitted that the relied-on art provides no such blaze marks for the trail.

The Action also has not addressed the added stability obtained in this invention from the absence of the usually present cysteines at positions 48 and/or 107 when a C-terminal or N-terminal cysteine is also present. That point is neither taught nor suggested by any of the art, let alone Pumpens and Zlotnick. This basis for rejection should therefore be withdrawn.

2. Second Rejection

Claims 7, 15 and 29 were again rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens et al. (1995) in view of Zlotnick et al. (1997) as applied previously and further in view of Nassal et al. (1992) (hereinafter Nassal). The rejection is respectfully traversed.

The present Action has asserted that the prior rejection is maintained "because Applicant has not presented evidence showing that there was no reasonable expectation of success." It is respectfully submitted that such evidence is only needed once a *prime facie* case of obviousness is made, and here such a case has not been made.

As pointed out in *In re Fine*, 5 USPQ2d 1596, 1598 (Fed Cir 1988), the Patent Office can satisfy its burden in establishing a *prime facie* case of obviousness "by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." [Citations omitted.] That is, blaze marks for the trail are needed. As the present and prior Replies show, the prior Action did not provide the blaze mark teachings, and as a consequence, the Patent Office did not meet its burden in establishing a *prime facie* case of obviousness.

Once again, neither Pumpens nor Zlotnick teaches anything about added stability of a chimer when the natural cysteines at positions 48 and 107 are removed and a further stabilizing cysteine is present at either or both of the N- and C-termini. Nassal suggests that HBc chimers would be more stable with the cysteines at 48 and 107 present, and that is contrary to the claimed subject matter.

Nassal says nothing about adding back two cysteines at the recited positions 76 and 82, and contains no disclosure concerning maintaining the cysteine deletions at 48 and 107, while adding cysteines at 76 and 82. Nassal also has no prediction concerning the effect of internal sequence additions. As such, this rejection should be withdrawn.

Still further, even if one were to agree for purposes of argument that a case of *prime facie* obviousness has been made here, the Court in *In re Papesch*, 137 USPQ 43, 51 (CCPA 1963), held that "[f]rom the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." Thus, the enhanced stabilities obtained when one or both cysteines at positions 48 and 107 are replaced and one or more Cys residues is added to a HBc sequence were unexpected and unpredicted by anything in the relied-on art. As such, the rejection should again be withdrawn.

3. Third Rejection

Claims 2, 17, 30 and 31 were again rejected as allegedly obvious from the combined disclosures of Zlotnick (above) in view of Nierynck et al., (1998) *Nature Medicine* **5(10):**1157-1163 (hereinafter Nierynck). The Nierynck paper teaches the use of the extracellular region of the M2 protein (M2e) fused to the N-terminus of full length HBc. The region of

the M2 protein utilized provided two cysteines near the N-terminus of the resulting chimer that therefore contained two Cys residues near the N-terminus and one Cys at C-terminal position 183. Zlotnick is as described previously. The Action asserts that it would have been obvious to combine the two teachings "because Zlotnick teaches the production of more stable hepatitis B core particles via addition of C-terminal cysteine with concomitant removal of internal cysteine residues..." This basis for rejection cannot be agreed with and is respectfully traversed.

The Action asserted that it is improper to attack the relied-on teachings individually where the rejections are based on a combination of teachings, citing two cases: *In re Keller*, 208 USPQ 871 (CCPA 1981) and *In re Merck & Co.*, 231 USPQ 375 (Fed. Cir. 1986). Both cases are good law, but inapplicable here. It is submitted that analyzing the relied-on art for what it actually teaches or suggests, and finding a fair reading of the summed teachings/suggestions to be wanting as has been done here is not what was held improper in *Keller*. Further, in the *Merck* case, a known compound with known psychotropic properties and a structure chemically similar to another known psychotropic drug was suggested in a prior art document to have the properties and use that were recited in the claims. Here, a chimer of the claims is new, and no art disclosure made any predictions about it. Thus, *Merck* is not applicable here on its facts.

The present and prior Actions have taken two disparate teachings and combined them to try to make them resemble the claimed subject matter, but that combination fails to duplicate a claimed chimer, and there is no teaching or suggestion in the art to make the proper modifications to arrive at a claimed

chimer. Thus, as noted above, Zlotnick teaches removal of all of the internal cysteines in a truncated chimer designated as Cp*149 and the same replacement plus the addition of a C-terminal Cys in the construct Cp*150. Zlotnick teaches no sequences added terminally or internally to his Cys-replaced HBc sequences. Nierynck teaches the use of the M2e polypeptide fused to the N-terminus of full length HBc that contained all of its internal Cys residues, including the C-terminal HBc Cys at position 183. There is no suggestion in Nierynck to use a truncated sequence, nor to replace any Cys residues, let alone the specific internal cysteines that are replaced in the claims.

It is respectfully submitted that there is no road map or blaze marks in either or both teachings to guide the skilled worker to arrive at a claimed chimer. Rather, the only directions are from the present application itself, and it cannot be used for that purpose. Fairly reading both teachings together does not lead to a claimed chimer.

Rather, one must manipulate both to arrive at a claimed chimer, and no independent instructions for those manipulations are present. Thus, as was the case for the proposed combination of Pumpens and Zlotnick, even if one summed the teachings to the two disclosures, the claimed subject matter does not come into being without exercise of still further manipulations that neither disclosure teaches or suggests.

It is thus submitted that this rejection should be withdrawn.

4. Fourth Rejection

Here, Claims 1-6, 8-14, 16-24, 26,31, and 33-42 were rejected over the disclosures of Jegerlehner as applied previously to claims 25, 27-28, 30, 32 and 43-46 in view of WO

01/9833 A2 to Page et al. (hereinafter Page). The Page teaching relates to a HBc chimer somewhat similar to that claimed here, but containing the cysteines at positions 48 and 107. The Jegerlehner teaching was discussed above and is basically a $Cys^{48}$ and $Cys^{107}$ mutated version of the HBc constructs discussed in Dr. Birkett's US Patent No. 6,231,864 that is discussed at page 8 of the present specification. This rejection is again respectfully traversed.

The present Action asserts that the previously noted misquotes were mere typographical errors. If that were the case, so be it. Typos happen to all of us, and are universally regretted.

Nonetheless, it is maintained that there is a difference in implication between what Page said and what the Action asserted it said. What Page said related to the native particles, whereas the Action's language was more general and implied a teaching that could include any chimer. As such, the prior Action did lead to "a molecule having a different structure".

The present Action directs applicant and counsel to the Summary of the Invention for a teaching in WO 01/98333 A2 that HBc "molecules as epitope carriers may be made more stable by the addition of C-terminal cysteines..." It is repeatedly submitted that there is no such teaching. Counsel has examined the Summary of the Invention, and found no use of the phrase "more stable", and enhanced stability is one of the features of the claimed invention. Rather, the statement in Page is as was quoted in the prior Reply and at the bottom of page 13 in the present Action.

The present Action argues in paragraph 43, page 15, that "Applicant has not argued that this rejection is as a

combination of references" and again relied-on the *Keller* and *Merck & Co.* cases It is submitted, however, that the sentence preceding the sentence from the Reply quoted in the Action was "it is submitted that there is no suggestion other than this application to combine the teachings of these two or any other disclosures." There thus was a refutation of the aptness of the combination of teachings.

However, to augment that discussion, it is noted that a wide variety of HBc constructs form particles. Pumpens has that teaching. Even the Zlotnick truncated and all Cys-replaced construct Cp*149 formed capsid particles as is seen from the first sentence of the Results and Discussion at Zlotnick's page 9558. A point of the present invention is enhanced stability of those formed particles in the absence of two internal Cys residues. The deficiencies of the Jegerlehner teaching have already been discussed and it has been shown that those teachings are directed to an entity that is not claimed here. Furthermore, there are no blaze marks in either relied-on teaching to direct a skilled worker to a claimed construct nor is there motivation to make a claimed construct without using the present application and hind sight. It is again submitted that this rejection should be withdrawn.

G. Provisional Double Patenting Rejection

All of the claims were again provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the claims of five co-pending applications: (1) claims 1-78 of Serial No. 09/930,915; (2) claims 1-33 of Serial No.10/274,616; (3) claims 1-53 of Serial No. 10/787,734; (4) claims 98-109 of Serial No. 10/806,006 and claims 79-115 of Serial No. 10/806,006. It is believed that one of two latter

applications should be Serial No. 10/805,913 in that the same serial number was recited twice with claims of the two being nested. Clarification of the applications and claims would be appreciated. It is still believed that this rejection is premature.

H. Further Art

A new piece of art has come to counsel's attention. That disclosure is present in US Patent No. 6,964,769 to Sebbel et al. and assigned on its face to Cytos Biotechnology AG. The patent issued on November 15, 2005. Several of the inventors are noted as authors of the Jegerlehner article that has been discussed previously. The claimed subject matter is similar to the construct discussed in the Jegerlehner article. However, it is not known which HBV subtype was used in preparing the materials of the Jegerlehner article. The sequence recited in the claims (SEQ ID NO:158) is C-terminal truncated and appears by comparison to the sequences of Fig. 1 herein to be of the *adyw* subtype with one or more *ayw* residues. This document is noted on Form PTO SB/08A that is enclosed.

No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the undersigned after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in §1.56(c) more than three months prior to the filing of this information disclosure statement.

I. Summary

Claims 1, 11 and 25 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

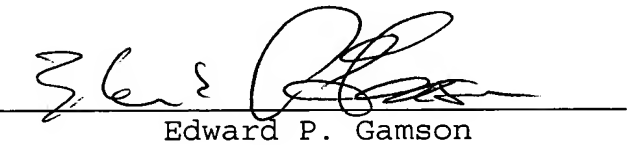
By _____
Edward P. Gamson, Reg. No. 29,381

WELSH & KATZ, LTD.
120 South Riverside Plaza, 22nd Floor
Chicago, Illinois 60606
Phone (312) 655-1500
Fax No. (312) 655-1501

Enclosures
- RCE
- Petition for 3-mo. Extension
- Check/Fee for RCE and Petition
- Form PTO-SB/08A w/art

CERTIFICATE OF MAILING

I hereby certify that this Reply and its stated enclosures, and a Petition for Extension of Time are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on August 17, 2006.

By 
Edward P. Gamson